REMARKS

This Amendment is filed in response to the Non-Final Office Action dated February 23, 2009. A Petition for a one month extension of time is submitted herewith this response. The Director is authorized to charge $130.00 for the petition for a one month extension of time and to credit any overpayment to Deposit Account No. 02-1818. If such a withdrawal is made, please indicate the Attorney Docket No. 0112701-00818 on the account statement.

Claims 1-3 and 6-8 are pending in the application. Claims 4-5 and 9-32 were previously canceled without prejudice or disclaimer. In the Office Action, Claims 1, 3 and 6-7 are rejected under 35 U.S.C. §102. Claims 1-3 and 6-8 are rejected under 35 U.S.C. § 112. In response, Applicants have amended Claims 1 and 6 and have canceled Claim 8 without prejudice or disclaimer. The amendments do not add new matter. In view of the amendments and/or for at least the reasons set forth below, Applicants respectfully submit that the rejection is improper and should be withdrawn.

In the Office Action, Claims 1, 3 and 6-7 are rejected under 35 U.S.C. §§102(a) and 102(e) as being anticipated by U.S. Publ. No. 2002/0115667 to Walkley et al. ("*Walkley*"). Claims 1, 3 and 6-7 are rejected under 35 U.S.C. §102(a) as being anticipated by Cell Death and Differentiation to Di Sano et al. ("*Di Sano*"). Claims 1, 3 and 6-7 are rejected under 35 U.S.C. §102(a) as being anticipated by Glycobiology to Deng et al. ("*Deng*"). Claims 1, 3 and 6-7 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Publ. No. 2002/0142985 to Dwek et al. ("*Dwek*"). Claims 1, 3 and 6-7 are rejected under 35 U.S.C. §102(b) as being anticipated by WO 01/36628 to Cabot et al. ("Cabot"). Claims 1, 3 and 6-7 are rejected under 35 U.S.C. §102(b) as being anticipated by Cell Death and Differentiation to Liu et al. ("Liu"). In contrast, Applicants respectfully submit that the cited references are deficient with respect to the present claims.

Currently amended independent Claim 1 recites, in part, a cosmetic product comprising an RNA polynucleotide antisense to a sequence comprising the glucosylceramide synthase mRNA. Currently amended independent Claim 6 recites, in part, a composition comprising an RNA polynucleotide antisense to a sequence comprised by the glucosylceramide synthase mRNA, and further comprising a cell containing the polynucleotide and a lower amount of the CD1d gene translation product than in similar cells lacking the polynucleotide. The amendments do not add new matter. The amendments are supported in the specification at, for example, page

12, lines 9-11; page 13, line 22-page 14, line 6. In the studies leading to the instant claims, Applicants surprisingly found that CD_{1d} gene transcription in mouse skin is responsive to external stress, such as UV radiation. This finding has been confirmed in human keratinocytes. In addition, it has been noted that skin CD_{1d} mediates UV-induced skin damage/inflammation by inducing COX-2 and TNF-α gene transcription and also inhibiting UV-induced apoptosis. Accordingly, CD_{1d} appears to negatively regulate apoptosis. Consequently, in cells under a stress situation, CD_{1d} supports a continued existence of the stressed cells, even when their genetic material is damaged or mutated. See, specification, page 7, line 26-page 8, line 6. However, genetic modification or deletion of glucosylceramide synthase mRNA to reduce the availability of glucosylceramides to CD_{1d} binding blocks the function of CD_{1d} to support the survival and propagation of damaged epidermal cells, thus preventing or treating epithelial tissue damage. As a result, epithelial tissue damage may be prevented or treated by using cosmetic compositions having an RNA polynucleotide antisense to a sequence comprising the glucosylceramide synthase mRNA. See, specification, page 8, lines 4-6; page 8, lines 7-8; and page 10, lines 13-15. In contrast, Applicants respectfully submit that *Walkley, Di Sano, Deng, Dwek, Cabot* and *Liu* all fail to disclose or suggest each and every element of the present claims.

Applicants initially note that currently amended independent Claim 6 now includes the subject matter of dependent Claim 8, which was not rejected in the Office Action as anticipated by any of the cited art. Applicants respectfully submit that dependent Claim 8 was not rejected as anticipated because the cited art fails to disclose or suggest a composition comprising an RNA polynucleotide antisense to a sequence comprised by the glucosylceramide synthase mRNA, and further comprising a cell containing the polynucleotide and a lower amount of the CD1d gene translation product than in similar cells lacking the polynucleotide as is now required, in part, by independent Claim 6. Accordingly, Applicants respectfully submit that Claims 6-7 are novel, nonobvious and distinguishable from the cited reference and are in condition for allowance.

With respect to independent Claim 1 and the dependent claims that depend therefrom, *Walkley, Di Sano, Deng, Dwek, Cabot* and *Liu* all fail to disclose or suggest a cosmetic product comprising an RNA polynucleotide antisense to a sequence comprising the glucosylceramide synthase mRNA as required, in part, by the present claims. Instead, and in contrast to the presently claimed cosmetic products, most of the cited references appear to be directed to pharmaceutical compositions.

As discussed in the specification, cosmetic products include, but are not limited to, products such as, for example, lotions, shampoos, creams, sun-screens, after-sun creams, sun-blockers, anti-ageing creams, ointments and/or anti-hair loss liquids, etc. The specification also discusses that the use of the presently claimed products is advantageous for essentially blocking CD_{1d} function in the skin and preventing the adverse effect of sun radiation, photo-ageing and exposure of the skin to free radicals. Thus, by providing a cosmetic product such as sun-screen, which contains a substance as claimed herein, a protection to the sun may be provided, which far exceeds anything known in the art. This feature is based in particular on the fact that the objective substance will penetrate the skin and exert its effect after having reached the target molecules. Since this effect will stay for a while, protection to the sun will even be present in case the sun-screen has been rubbed off or has been washed off. Yet, apart from sun-screens the objective substances may be included in common day-creams, lotions, etc. to prevent negative effects of the daily environment, including pollution, oxidative stress, etc. It will be appreciated that the present cosmetic products will contain a mixture of different ingredients known to the skilled person, ensuring a fast penetration of the objective substance into the skin and preventing degradation thereof during storage. See, specification, page 12, lines 9-11; page 13, line 22-page 14, line 6.

The above-described cosmetic products are in contrast to pharmaceutical compositions which are generally referred to as medicine or a medicament, and can be loosely defined as any substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. See, Wikipedia, "pharmaceutical drug." More specifically, pharmaceuticals are generally medications which control bodily processes internally. In contrast, cosmetics are generally known to manipulate the body from the outside, cosmetically improving appearances. Further, pharmaceuticals are heavily regulated by the Food and Drug Adminstration, while cosmetic products are generally not government regulated because they are not considered a device that alters bodily chemistry of function internally in any way. Cosmetics are also not advertised as substances that change the chemistry of the body. Accordingly, the cosmetic products of the present claims can be distinguished from the pharmaceutical compositions of the prior art.

For example, *Walkley* is entirely directed to administration of pharmaceutical compositions through various delivery systems including intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural and oral routes. See, *Walkley*,

page 4, [0040]. However, at no place in the disclosure does *Walkley* disclose or suggest the use of cosmetic products.

Di Sano is entirely directed to studies to find out if antisense to glucosylceramide synthase in human neuroepithelioma affects cell growth but not apoptosis. *Di Sano* also looks at whether downregulation of glucosylceramide syntase expression potentiated the apoptotic response of CHP-100 cells to various cytotoxic agents. See, *Di Sano*, Title; page 695, column 1, lines 7-9. However, at no place in the disclosure does *Di Sano* disclose or suggest the use of cosmetic products.

Deng is entirely directed to studies regarding whether transfection of glucosylceramide synthase antisense inhibits mouse melanoma formation. *Deng* discloses that the study findings demonstrate that stable transfection of glucosylceramide synthase antisense reduces cellular glycosphingolipid levels and reduces tumorigenicity. See, *Deng*, Title; page 145, column 1, Abstract. However, at no place in the disclosure does *Deng* disclose or suggest the use of cosmetic products. Instead, *Deng* merely discusses the transfection of MEB4 melanoma cells with an antisense sequence to the gene encoding glucosylceramide synthase. See, *Deng*, page 145, column 2, last paragraph.

Dwek is entirely directed to administration of pharmaceutical compositions through various delivery systems including intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural and oral routes. See, *Dwek*, page 4, [0050]. However, at no place in the disclosure does *Dwek* disclose or suggest the use of cosmetic products.

Cabot is entirely directed toward compositions for reversing the drug resistance of cancer cells. See, *Cabot*, Abstract. Indeed, *Cabot* is entirely directed toward pharmaceutical compositions that may be dissolved or dispersed in a pharmaceutically acceptable carrier or aqueous medium. See, *Cabot*, page 15, lines 25-32. The compositions are formulated for parenteral administration via injection. See, *Cabot*, page 16, lines 1-17. Therefore, at no place in the disclosure does *Cabot* disclose or suggest the use of cosmetic products.

Liu is entirely directed to studies to determine whether uncoupling ceramide glycosylation by transfection of glucosylceramide synthase antisense reverses adriamycin resistance. *Liu* discloses that asGCS is introduced into adriamycin-resistant human breast cancer cells to study its effects on adriamycin resistance. See, *Liu*, Title; page 7138, column 2,

paragraph 2. However, at no place in the disclosure does *Liu* disclose or suggest the use of cosmetic products.

Accordingly, *Walkley, Di Sano, Deng, Dwek, Cabot* and *Liu* all fail to disclose or suggest a cosmetic product comprising an RNA polynucleotide antisense to a sequence comprising the glucosylceramide synthase mRNA as required, in part, by the present claims.

Further, anticipation is a factual determination that "requires the presence in a single prior art disclosure of each and every element of a claimed invention." *Lewmar Marine, Inc. v. Barient, Inc.*, 827 F.2d 744, 747 (Fed. Cir. 1987) (emphasis added). Federal Circuit decisions have repeatedly emphasized the notion that anticipation cannot be found where less than all elements of a claimed invention are set forth in a reference. See, *e.g.*, *Transclean Corp. v. Bridgewood Services, Inc.*, 290 F.3d 1364, 1370 (Fed. Cir. 2002). As such, a reference must clearly disclose each and every limitation of the claimed invention before anticipation may be found. For at least these reasons, Applicants respectfully submit that *Walkley, Di Sano, Deng, Dwek, Cabot* and *Liu* all fail to anticipate the presently claimed subject matter.

For at least the reasons discussed above, Applicants respectfully submit that Claims 1, 3 and 6-7 are novel, nonobvious and distinguishable from the cited reference and are in condition for allowance.

Therefore, Applicants respectfully request that the rejections of Claims 1, 3 and 6-7 under 35 U.S.C. §102 as anticipated be reconsidered and withdrawn.

In the Office Action, Claims 1-3 and 6-8 are rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the enablement requirement. Specifically, the Patent Office suggests that there is lack of support in the specification for compositions comprising a polynucleotide antisense to glucosylceramide synthase mRNA and compositions that treat or prevent epithelial tissue damage. In support of this contention, the Patent Office suggests that there exists no relation between the claimed composition and treating or preventing epithelial tissue damage. In contrast, however, Applicants disagree with the Patent Office's conclusion of lack of enablement and request that the rejections be reconsidered and withdrawn.

An analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the

enablement requirement is whether the experimentation needed to practice the invention is undue or unreasonable. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). Applicants respectfully submit that one having ordinary skill in the art would readily be capable of performing the claimed method without undue experimentation.

The claims are directed, in part, toward the use of compositions comprising a polynucleotide antisense to glucosylceramide synthase mRNA and compositions for treating or preventing epithelial tissue damage. The specification sufficiently teaches, and it is well known in the art, that glucosylceramide synthase is associated with epithelial tissue damage, that the regulation of glucosylceramides in maintaining epithelial cell homeostasis is related to preventing/treating epithelial damage by silencing glucosylceramide synthase expression, and that reducing epithelial cell proliferation is related to preventing/treating epithelial damage. Indeed, the claimed method can be easily practiced without undue experimentation. Accordingly, Applicants respectfully submit that the skilled artisan could make and/or use the invention from the disclosure in the specification without undue experimentation.

The survival and propagation of epidermal cells damaged and/or mutated by stress in the form of UV radiation, pollutants, free radicals, chemical substances and the like leads to epithelial tissue damage. See, specification, page 4, lines 3-4 and page 8, lines 9-18. Whether the damaged cells survive and propagate depends on a balance between proliferation, differentiation and apoptosis of epidermal cells. See, specification, page 7, lines 28-29. This balance is regulated by lipids. See, specification, page 7, line 30. In particular, ceramides inhibit cellular proliferation and induce cellular differentiation and programmed cell death. Conversely, glucosylceramides promote cellular proliferation and prevent cellular differentiation and programmed cell death. See, specification, page 8, lines 4-6. CD_{1d} supports the continued existence of stressed cells by binding glucosylceramide. See, specification, page 8, lines 7-8 and page 10, lines 13-15. Glucosylceramide synthase converts ceramides into glucosylceramides. Therefore, genetic modification or deletion of the glucosylceramide synthase mRNA to reduce the availability of glucosylceramides to CD_{1d} binding blocks the function of CD_{1d} to support the survival and propagation of damaged epidermal cells, thus preventing or treating epithelial tissue damage. That glucosylceramide synthase converts ceramides into glucosylceramides and that CD_{1d} binds to glucosylceramides are well known in the art.

More specifically, the specification clearly states that CD_{1d} appears to negatively regulate cell apoptosis such that CD_{1d} supports a continued existence of stressed cells (*e.g.*, cells exposed to UV radiation), even when the genetic material of the cell is damaged and/or mutated, which damaged cells will continue to induction of inflammation processes and eventually account for the phenomenon of ageing or, eventually, tumor development. See, specification, page 7, line 26-page 8, line 6. Therefore, in blocking apoptosis and/or modifying endogenous CD_{1d} function, apoptosis of cells under stress may be promoted, instead of their survival and propagation. See, specification, page 8, lines 14-17.

Further, the Patent Office admits that the glucosylceramide synthase mRNA sequence and antisense technology were both known in the art at the time of the invention. See, Final Office Action dated May 1, 2008, page 3, lines 16-18. As such, it must follow that the sequence for glucosylceramide synthase was also known to be capable of binding to the glucosylceramide synthase mRNA sequence to prohibit the translation of the glucosylceramide synthase mRNA into glucosylceramide synthase.

Glucosylceramide synthase is generally known in the art to be a pivotal enzyme in the biosynthesis of, and catalyses the transfer of, glucose from UDP-glucose (UDP-Glc) to ceramide to form glucosylceramide (GlcCer), the common precursor of most higher-order glycosphingolipids. Therefore, glucosylceramide synthase is critical to the production of GlcCer.

GlcCer is known to be capable of blocking and/or modifying biological CD_{1d} function (*e.g.*, GlcCer is capable of blocking the CD_{1d} receptors from binding with natural killer T-cells and, thus, reduces or prevents inflammatory and/or immunosuppressive reactions). See, specification, page 11, lines 5-26. The specification clearly states that "ceramides are associated with inhibition of cellular proliferation, induction of cellular differentiation and programmed cell death. In contrast, GlcCer induce cell proliferation and inhibit programmed cell death." See, specification, page 7, line 26-page 8, line 6. Thus, since GlcCer is able to block and/or modify biological CD_{1d} function, GlcCer is capable of promoting apoptosis, which is desirable in instances where cells have experienced damage but are capable of proliferating to potentially cause ageing and/or tumor development. It would be beneficial, instead, for such stressed cells to be terminated to reduce or eliminate the risk of aging and/or tumor development.

Therefore, based on the above information, it must follow that an RNA polynucleotide antisense to a sequence comprising the glucosylceramide synthase mRNA is capable of binding to the glucosylceramide synthase mRNA to prohibit the formation of glucosylceramide synthase, which will, in turn, reduce or eliminate the production of glucosylceramide. The reduction or elimination of glucosylceramide will, in turn, reduce damaged cell proliferation thereby preventing or treating epithelial tissue damage as is required, in part, by the present claims. For at least these reasons, Applicants respectfully submit that it is only with a misunderstanding of the present claims, specification and/or state of the art at the time of filing of the present application that the Patent Office is able to maintain the present enablement rejection.

Moreover, Applicants reiterate that the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the art without undue or unreasonable experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). Further, compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, does not turn on whether an example is disclosed. See MPEP 2164.02. An example may be "working" or "prophetic." A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved. *Id.* Accordingly, Applicants need not have actually reduced the invention to practice prior to filing and the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 (CCPA 1970). Nevertheless, Applicants have provided examples in the specification supporting the practice of the present claims.

While the application may not disclose working examples of tests performed using the presently claimed substances and methods with humans, Applicants respectfully submit that this is not dispositive. For example, it is generally accepted in the art that mice are proven experimental models for determinations as to possible effects of new drugs and compounds for use in humans. In this case, the teachings and examples disclosed in Applicants' specification teach the skilled artisan how to make and use the claimed invention for treatment of mice using the presently claimed substances. Indeed, the examples found at pages 54-75 support a role for

CD_{1d} in the regulation of phospholipid metabolism which controls inflammatory processes. The examples also demonstrate that blocking CD_{1d} upregulates genes trolling hair follicle development, and down-regulates genes involved in inflammation and cancer development. Consequently, one having ordinary skill in the art can reasonably conclude that by administering the compositions of the present claims to human subjects, CD_{1d} may act to down-regulate genes involved in inflammation and cancer development in accordance with the present claims. In fact, the specification even states that it has been surprisingly found that CD_{1d} gene transcription in mouse skin is responsive to external stress, such as UV radiation, which finding has been confirmed in human keratinocytes. See, specification, page 7, lines 21-23 (emphasis added). Accordingly, Applicants respectfully disagree with the Patent Office's statement that "[applicants] have failed to show how or why the CD1d-relevant working examples provide sufficient guidance and direction to one of ordinary skill in the art to make and use the claimed invention without undue experimentation.'" See, Office Action, page 10, lines 15-17.

Although CD_{1d} is not the claimed target gene, as noted by the Patent Office in the Advisory Action at page 2, line 11, CD_{1d} is one of the receptors via which the previously mentioned lipids fulfill their biological task. Specifically, CD_{1d} seems to negatively regulate apoptosis such that CD_{1d} supports a continued existence of stressed cells (*e.g.*, cells exposed to UV radiation), even when the genetic material of the cell is damaged and/or mutated, which damaged cells will continue to induction of inflammation processes and eventually account for the phenomenon of ageing or, eventually, tumor development. See, specification, page 7, line 26-page 8, line 6. Therefore, in blocking apoptosis and/or modifying endogenous CD_{1d} function by eliminating or reducing the availability of glucosylceramides to CD_{1d} binding, apoptosis of cells under stress may be promoted, instead of their survival and propagation. See, specification, page 8, lines 14-17. Accordingly, while the target gene may not be CD_{1d}, the presently claimed compositions are effective in blocking apoptosis and/or modifying endogenous CD_{1d} function.

Similarly, the activity of regulatory molecules that control epithelial homeostasis such as ceramides and/or glucosylceramides, may be modified such that they also exert the desired effect on the CD_{1d} molecule. To this end, the number of the glucosylceramide synthase transcripts may be reduced by designing a polynucleotide antisense to at least a part of the glucosylceramide synthase gene or glucosylceramide synthase mRNA, so that eventually the signal to epithelial cells to proliferate is turned down. See, specification, page 10, lines 13-24.

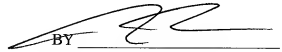
Therefore, based on at least the information set forth above, which contains information that was known in the art and information that is disclosed in the specification, Applicants respectfully submit that the skilled artisan would be able to practice the present invention without undue experimentation.

Accordingly, Applicants respectfully submit that Claims 1-3 and 6-8 fully comply with 35 U.S.C. §112, first paragraph, and are in condition for allowance.

For the foregoing reasons, Applicants respectfully request reconsideration of the above-identified patent application and earnestly solicit an early allowance of same. In the event there remains any impediment to allowance of the claims which could be clarified in a telephonic interview, the Examiner is respectfully requested to initiate such an interview with the undersigned.

Respectfully submitted,

K&L GATES LLP



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